

A Randomized Placebo-Controlled Trial of Rasagiline in Levodopa-Treated Patients With Parkinson Disease and Motor Fluctuations

The PRESTO Study

Parkinson Study Group

Background: Rasagiline (N-propargyl-1[R]-aminoindan) mesylate is a novel irreversible selective monoamine oxidase type B inhibitor, previously demonstrated to improve symptoms in early Parkinson disease (PD).

Objective: To determine the safety, tolerability, and efficacy of rasagiline in levodopa-treated patients with PD and motor fluctuations.

Design: Multicenter, randomized, placebo-controlled, double-blind, parallel-group study.

Patients: Parkinson disease patients (N=472) with at least 2½ hours of daily “off” (poor motor function) time, despite optimized treatment with other anti-PD medications.

Interventions: Rasagiline, 1.0 or 0.5 mg/d, or matching placebo.

Main Outcome Measures: Change from baseline in total daily off time measured by patients’ home diaries during 26 weeks of treatment, percentage of patients

completing 26 weeks of treatment, and adverse event frequency.

Results: During the treatment period, the mean adjusted total daily off time decreased from baseline by 1.85 hours (29%) in patients treated with 1.0 mg/d of rasagiline, 1.41 hours (23%) with 0.5 mg/d rasagiline, and 0.91 hour (15%) with placebo. Compared with placebo, patients treated with 1.0 mg/d rasagiline had 0.94 hour less off time per day, and patients treated with 0.5 mg/d rasagiline had 0.49 hour less off time per day. Prespecified secondary end points also improved during rasagiline treatment, including scores on an investigator-rated clinical global impression scale and the Unified Parkinson’s Disease Rating Scale (activities of daily living in the off state and motor performance in the “on” state). Rasagiline was well tolerated.

Conclusions: Rasagiline improves motor fluctuations and PD symptoms in levodopa-treated PD patients. In light of recently reported benefits in patients with early illness, rasagiline is a promising new treatment for PD.

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MOTOR COMPLICATIONS, especially “on-off” fluctuations and dyskinesias, commonly occur in patients with Parkinson disease (PD) after months to years of dopaminergic therapy.¹ Despite the availability of several new treatments, the emergence and progression of these motor complications continue to represent

brain, can potentiate the beneficial motor effect of levodopa³⁻⁵ and attenuate motor fluctuations.⁶⁻⁹

Rasagiline (N-propargyl-1[R]-aminoindan) mesylate is a novel irreversible MAO-B inhibitor with high selectivity for the B isoform of the enzyme. Rasagiline, 1.0 mg/d, causes almost total inhibition of platelet MAO-B in humans.¹⁰ We recently reported a multicenter, randomized, double-blind, placebo-controlled clinical investigation of rasagiline monotherapy in 404 subjects with early, otherwise untreated, PD.^{11,12} Rasagiline was well tolerated at dosages of 1.0 and 2.0 mg/d, and patients receiving rasagiline had better function after 6 months of treatment than those receiving placebo. In the present study, we evaluated the safety, tolerability, and efficacy of

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Group Information: A list of the members of the Parkinson Study Group who participated in this study and were authors of this report appears on page 246.

major unmet therapeutic needs in many PD patients.² Previous studies have demonstrated that inhibitors of monoamine oxidase type B (MAO-B), the main enzyme that metabolizes dopamine in the

rasagiline compared with placebo in levodopa-treated patients with motor fluctuations.

METHODS

ORGANIZATION

The study was designed, implemented, and analyzed by the Parkinson Study Group in collaboration with Teva Pharmaceutical Industries, Ltd, Netanya, Israel, and H. Lundbeck A/S, Copenhagen, Denmark. It was reviewed and approved by the institutional review boards at each of the participating centers.

PATIENTS

Levodopa-treated patients with motor fluctuations (N=472) were enrolled at 57 participating Parkinson Study Group sites between December 2000 and June 2002. Eligible patients included those with idiopathic PD who were in a modified Hoehn and Yahr¹³ stage of less than 5 in the "off" (poor motor function) state, were 30 years or older, and experienced at least 2½ hours in the off state daily, as confirmed by a baseline 3-day home diary. Patients must have received an optimized and stable dosage of levodopa at least 3 times daily, not including a bedtime dose, for at least 2 weeks before their screening evaluation. Concomitant treatment with stable dosages of dopamine agonists, amantadine hydrochloride, anticholinergics, and entacapone was allowed. Patients with atypical or secondary parkinsonism, pronounced cognitive impairment (Mini-Mental State Examination¹⁴ score, <24), depressive symptoms (Beck Depression Inventory¹⁵ score, >15), and unstable neurological and medical disorders were excluded.

PROCEDURES

This was a multicenter, randomized, placebo-controlled, double-blind study of parallel groups of PD subjects with motor fluctuations while receiving optimized levodopa therapy. Following a screening visit to ensure that subjects met all enrollment criteria, including the ability to complete accurate home diaries, patients were randomized to 0.5 mg/d rasagiline, 1.0 mg/d rasagiline, or matching placebo. The computer-generated randomization plan provided for stratification by center and blocking to ensure approximate balance among the treatment groups within each center. The levodopa dosage could be decreased during the first 6 weeks of the study at the discretion of the investigator but was held constant for the last 20 weeks of the study. Subjects had visits 3, 6, 10, 14, 20, and 26 weeks after baseline for safety and efficacy monitoring. A home diary in which subjects rated themselves every half hour as "on without dyskinesias or on without troublesome dyskinesias," "on with troublesome dyskinesias," "off," or "asleep" was completed for 3 days immediately before the baseline, week 6, week 14, and week 26 visits. Definitions of "on" ("relatively good overall function and mobility when you feel your medication is working"), off ("relatively poor overall function . . . which corresponds to when your medication is not working"), dyskinesias ("involuntary, nontremor movements"), and troublesome dyskinesias (those that are "painful, impair balance, or are excessive to the point of causing impairment in coordination or general function") were explained and demonstrated using a standardized video training tape and practice diaries. Subjects monitored blood pressures before and after the main meal of the day for 7 days before the baseline, week 3, and week 26 visits using an automated device (Welch Allyn, Skaneateles, NY). Urinalysis, complete blood counts, and serum chem-

istry profiles were performed at screening and after 10 and 26 weeks of treatment at a central facility (ACM Laboratories, Rochester, NY). Electrocardiograms (ECGs) were performed at screening and after 26 weeks of treatment. Dermatologic examinations were performed at screening and after 14 and 26 weeks of treatment because of the increased frequency of skin cancers in PD in general^{16,17} and the occurrence of a few cases in prior rasagiline investigations.¹² Patients were not required to restrict tyramine intake at any time.

OUTCOME MEASURES

The prespecified primary measure of efficacy was the change from baseline in mean total daily off time, as measured by home diaries, averaged during the treatment period (from weeks 6, 14, and 26). Secondary measures of efficacy, in prespecified order for purposes of statistical analysis, included the investigator's clinical global impression of patient improvement during the study as measured on a 7-point scale (ranging from "significantly improved" to "no change" to "significantly worsened"), as well as changes from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS)¹⁸ activities of daily living (ADL) subscale during off periods, in the UPDRS motor subscale during on periods, and in patient-rated quality of life as measured by the Parkinson Disease Quality-of-Life (PDQUALIF) scale.¹⁹ Additional prespecified end points included changes from baseline in the mean total daily on time, in the Schwab and England²⁰ ADL scale during on and off periods, and in the UPDRS ADL subscale during on periods. Measures of safety included the frequency and severity of reported adverse experiences, changes in vital signs, laboratory test results, ECGs, and dermatologic examinations. Changes in laboratory and ECG values were considered abnormal when they deviated from reference ranges established by the central laboratories. Systolic blood pressure was considered abnormal when greater than 180 mm Hg, less than 90 mm Hg, or changed by more than 30 mm Hg from baseline. Diastolic blood pressure was considered abnormal when greater than 100 mm Hg, less than 50 mm Hg, or changed by more than 20 mm Hg from baseline. Pulse rate was considered abnormal when greater than 120 beats/min, less than 45 beats/min, or changed by more than 20 beats/min from baseline. Tolerability was assessed based on the number of patients in each group who discontinued the study.

STATISTICAL ANALYSIS

The intended sample size of 150 patients per group (total sample, 450) was chosen to provide 80% or better power to detect an improvement of 45 minutes or more in the mean total daily off time in either active treatment group compared with the placebo group. The primary analysis of efficacy used an analysis of covariance model that included the change from baseline in the mean total daily off time as the dependent variable, treatment group as the independent variable of interest, investigator (center) as a stratification factor, and baseline off time as a covariate. The treatment × center interaction was to be included if significant at $P < .10$. The primary statistical analysis included data from all patients with postrandomization diary data (n=451). To determine the effect of patient withdrawals, the analyses were repeated with only patients who completed the study (n=414) and patients who completed all procedures according to protocol (n=359). The results of the latter analyses did not differ materially from those of the primary analyses and hence are not reported. Secondary and exploratory efficacy measures were analyzed in the same way as the primary measure of efficacy. If a patient was missing a response, the last

available observation for that patient was carried forward and imputed for that visit. Frequencies of adverse experiences and abnormal laboratory test values, vital signs, and ECG results were analyzed by χ^2 tests, with imbalances among treatment groups flagged at a nominal $P < .05$.

All methods of analysis were prespecified before patient treatment assignments were revealed. Analyses were performed according to the intention-to-treat principle, and $P < .05$ was used for formal significance testing and interval estimation.

A hierarchical method of analysis, combined with the step-up modification to the Bonferroni method by Hochberg,²¹ was used to control for type I error. Analyses of the primary outcome measure (change in the mean total daily off time) and the 4 prespecified and ordered secondary outcome measures (clinical global impression, change in the UPDRS ADL subscale during off time, change in the UPDRS motor subscale during on time, and change in the PDQUALIF scale) were designed to use 2 types of contrasts (1.0 mg/d vs placebo and 0.5 mg/d vs placebo, for a maximum of 5 contrasts for each rasagiline dosage). The hierarchical approach for each dosage tested the 5 outcomes in their prespecified order (as listed), with the testing for that dosage to be terminated at the first nonsignificant result.²²

RESULTS

PATIENT CHARACTERISTICS, DISPOSITION, AND COMPLIANCE

Treatment groups had no significant differences at baseline with regard to demographic and clinical characteristics (**Table 1**). **Figure 1** tracks all evaluated patients, by treatment group, through the study. Overall, 414 patients (87.7% of enrolled) completed 26 weeks of treatment. A subset of 359 patients (76.1% of enrolled) completed the study without deviating from the protocol. The most common deviations were premature termination (12%), fewer than 6 acceptable daily diaries (10%, mainly in patients who terminated prematurely), and change in daily levodopa or other anti-PD medication dosage by more than 20% from baseline during the last 20 weeks of the study (4%). Compliance was high, as measured by pill counts, with 95% of patients taking at least 90% of scheduled doses. Between baseline and the week 26 visit, patients receiving placebo decreased their mean \pm SD daily levodopa dosages by 12 ± 142 mg, patients receiving 0.5 mg/d of rasagiline decreased their dosages by 32 ± 122 mg, and patients receiving 1.0 mg/d rasagiline decreased their dosages by 36 ± 133 mg. In each group, the median change in levodopa dosage was 0 mg. Most patients were taking additional PD medications, including dopamine agonists, entacapone, and amantadine (Table 1).

EFFICACY

During the treatment period, the mean adjusted total daily off time decreased from baseline by 1.85 hours (29%) in patients treated with 1.0 mg/d of rasagiline, 1.41 hours (23%) with 0.5 mg/d rasagiline, and 0.91 hour (15%) with placebo (**Table 2**). Patients treated with 1.0 mg/d of rasagiline had 0.94 hour (95% confidence interval, 0.51-1.36 hours; $P < .001$) less off time per day compared with

Table 1. Patient Characteristics at Baseline*

Characteristic	Placebo (n = 159)	Rasagiline	
		0.5 mg/d (n = 164)	1.0 mg/d (n = 149)
Age, y	64.5 (9.9)	62.6 (9.5)	62.9 (8.9)
Male sex†	104 (65.4)	102 (62.2)	99 (66.4)
Disease duration, y	9.7 (4.9)	9.3 (5.6)	8.8 (5.4)
Time on levodopa, y	8.5 (4.7)	8.3 (5.5)	7.9 (5.4)
Daily levodopa dosage, mg	821 (485)	750 (379)	815 (471)
Concomitant medication use†			
Dopamine agonists	111 (69.8)	116 (70.7)	107 (71.8)
Entacapone	65 (40.9)	55 (33.5)	54 (36.2)
Amantadine	38 (23.9)	33 (20.1)	27 (18.1)
Daily off time, h	6.0 (2.2)	6.0 (2.0)	6.3 (2.6)
Daily on time, h			
Without dyskinesias	9.8 (2.6)	9.5 (2.6)	9.4 (3.0)
With dyskinesias	1.0 (1.7)	1.1 (2.2)	1.0 (2.0)
Hoehn and Yahr stage during on time	2.1 (0.7)	2.0 (0.6)	2.0 (0.6)
Investigator-rated Schwab and England ADL score			
During on time	88.1 (8.6)	88.8 (8.1)	88.3 (11.1)
During off time	70.7 (15.1)	72.1 (15.1)	71.0 (17.2)
UPDRS score			
Total on time	28.5 (14.5)	28.9 (16.0)	28.2 (15.3)
Motor performance during on time	20.7 (10.3)	21.4 (12.0)	20.8 (11.0)
ADL during on time	6.1 (5.1)	5.6 (4.8)	5.8 (5.0)
ADL during off time	15.5 (5.7)	15.7 (6.6)	15.6 (6.8)
MMSE score	29.0 (1.3)	28.9 (1.3)	29.0 (1.3)

Abbreviations: ADL, activities of daily living; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale.

*Data are given as mean (SD) unless otherwise indicated. Potential ranges are 0 to 5 for the Hoehn and Yahr stage, 0 to 100 for the Schwab and England ADL score, 0 to 176 for the UPDRS total score, 0 to 108 for the UPDRS motor score, 0 to 52 for the UPDRS ADL score, and 0 to 30 for the MMSE score.

†Data are given as number (percentage).

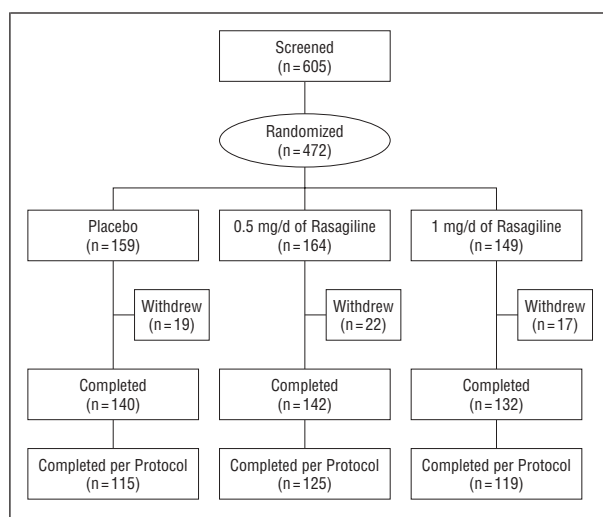


Figure 1. Patient disposition through screening, randomization, and 26 weeks of double-blind treatment.

placebo. Patients treated with 0.5 mg/d of rasagiline had 0.49 hour (95% confidence interval, 0.08-0.91 hour; $P = .02$) less off time compared with placebo. Changes from

Table 2. Efficacy End Points*

Change From Baseline	Rasagiline, 0.5 mg/d vs Placebo		Rasagiline, 1.0 mg/d vs Placebo	
	Mean (95% CI)	P Value	Mean (95% CI)	P Value
Primary end point of off time	-0.49 (-0.91 to -0.08)	.02	-0.94 (-1.36 to -0.51)	<.001
Secondary end points				
Clinical global impression	-0.39 (-0.64 to -0.13)	.003	-0.68 (-0.94 to -0.42)	<.001
UPDRS score				
ADL during off time	-1.20 (-2.08 to -0.32)	.008	-1.34 (-2.24 to -0.43)	.004
Motor performance during on time	-2.91 (-4.59 to -1.23)	<.001	-2.87 (-4.58 to -1.16)	.001
PDQUALIF summary score	-2.18 (-4.49 to 0.14)	.07	-1.48 (-3.86 to 0.90)	.22
Exploratory end points				
Daily on time				
Without dyskinesias	0.51 (0.00 to 1.03)	.050	0.78 (0.26 to 1.31)	.004
With dyskinesias*	-0.05 (-0.41 to 0.31)	.79	0.37 (0.00 to 0.74)	.048
Investigator-rated Schwab and England ADL score				
During off time	0.92 (-1.51 to 3.35)	.46	3.00 (0.49 to 5.51)	.02
During on time	0.96 (-0.69 to 2.61)	.25	0.63 (-1.06 to 2.33)	.46
UPDRS score†				
ADL during on time	-0.62 (-1.38 to 0.14)	.11	0.06 (-0.73 to 0.84)	.89
Dyskinesia*	0.24 (-0.08 to 0.57)	.14	0.37 (0.04 to 0.70)	.03
Postural instability and gait	-0.41 (-0.79 to -0.03)	.04	-0.07 (-0.46 to 0.32)	.73
Rigidity*	-0.51 (-1.07 to 0.06)	.08	-0.66 (-1.24 to -0.09)	.02
Bradykinesia	-0.58 (-1.43 to 0.27)	.18	-0.89 (-1.77 to -0.00)	.049
Tremor*	-0.79 (-1.25 to -0.33)	<.001	-0.73 (-1.20 to -0.27)	.002

Abbreviations: ADL, activities of daily living; CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale.

*Analysis includes the treatment × center interaction.

†Potential ranges are 0 to 12 for dyskinesia, 0 to 20 for postural instability and gait, 0 to 20 for rigidity, 0 to 36 for bradykinesia, and 0 to 32 for tremor.

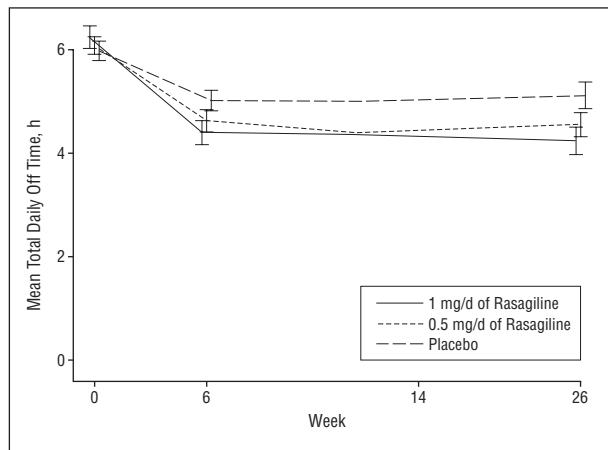


Figure 2. Mean total daily off time for subjects completing 26 weeks of treatment. Patients receiving 0.5 or 1.0 mg/d of rasagiline had a greater reduction in mean total daily off time compared with patients receiving placebo.

baseline and differences between groups were sustained throughout the treatment period (**Figure 2**). There was no evidence for differences in treatment effects at different sites ($P = .58$, treatment × center interaction).

Secondary efficacy measures were assessed using a pre-specified hierarchical analysis. Compared with placebo, the clinical global impression, UPDRS ADL score during off time, and UPDRS motor score during on time improved significantly during treatment in patients receiving either dosage of rasagiline (Table 2). Quality of life, as measured by the PDQUALIF summary score, showed a trend toward improvement in patients treated with 0.5 mg/d of rasagiline ($P = .07$) but not with 1.0 mg/d of

rasagiline. The social subscale of the PDQUALIF scale showed a benefit of both rasagiline dosages over placebo, the outlook subscale showed a benefit for the 0.5-mg/d dosage only, and the function, image, independence, sleep, and urinary subscales showed no difference from placebo.

Prespecified exploratory analyses (Table 2) demonstrated significant increases in the amount of on time per day during treatment with both dosages of rasagiline, corresponding to the decreases in off time. In the 0.5-mg/d rasagiline group, all of the increase in on time was without troublesome dyskinesias. In the 1.0-mg/d rasagiline group, 32% of the increase in on time included troublesome dyskinesias. Rasagiline, 1.0 mg/d, produced significant improvement in the Schwab and England²⁰ ADL scale during off times ($P = .02$), but 0.5 mg/d did not. Post hoc analysis of UPDRS subscores during on times revealed significant improvements in rigidity, bradykinesia, and tremor in patients treated with 1.0 mg/d of rasagiline (as rated on the UPDRS) and in postural instability and gait and tremor in patients treated with 0.5 mg/d.

SAFETY AND TOLERABILITY

The number of patients discontinuing for any reason, or because of an adverse event, was not significantly different between treatment groups ($P = .85$, χ^2 test) (Figure 1). Adverse events were reported in 87% of patients receiving placebo, 91% receiving 0.5 mg/d of rasagiline, and 95% receiving 1.0 mg/d of rasagiline. Adverse events that were significantly more common in patients treated with either dosage of rasagiline compared with placebo are

Table 3. Patients With Adverse Events During Treatment

Event	Placebo, No. (%) (n = 159)	Rasagiline			
		0.5 mg/d (n = 164)		1.0 mg/d (n = 149)	
		No. (%)	P Value*	No. (%)	P Value*
Weight loss	4 (2.5)	4 (2.4)	.76	14 (9.4)	.02
Vomiting	2 (1.3)	6 (3.7)	.31	10 (6.7)	.03
Anorexia	1 (0.6)	3 (1.8)	.64	8 (5.4)	.04
Balance difficulty	1 (0.6)	9 (5.5)	.03	5 (3.4)	.19

*Compared with placebo.

listed in **Table 3**. These mostly involved the gastrointestinal system and appeared to be dose related. Dyskinesias were reported as an adverse event in 10% of patients receiving placebo and 18% of patients receiving either dosage of rasagiline ($P = .03$, χ^2 test for combined rasagiline groups vs placebo). Balance difficulty occurred more often in patients receiving rasagiline, but it did not appear to be dose related. Depression was significantly less common in patients receiving 0.5 mg/d of rasagiline compared with placebo ($P = .04$). There were 22 serious adverse events in 14 patients receiving placebo, 42 in 21 patients receiving 0.5 mg/d of rasagiline, and 27 in 18 patients receiving 1.0 mg/d of rasagiline. The most common serious adverse events (all 3 groups combined) were related to accidental injury (n=6), arthritis, worsening PD, melanoma, stroke (n=3), and urinary tract infection (n=3); none were significantly more common in patients receiving rasagiline compared with placebo.

Rasagiline did not have adverse effects on blood pressure or pulse rate. Flagging group differences in the incidence of abnormalities at $P < .05$ revealed more patients with low systolic (20 patients vs 8 patients) or diastolic (9 patients vs 1 patient) blood pressure while standing, but not while supine, during treatment with 0.5 mg/d of rasagiline compared with placebo. Analogous comparisons between 1.0 mg/d of rasagiline and placebo did not demonstrate significant differences. More patients receiving placebo had increases in systolic blood pressure compared with baseline (standing: 28 patients receiving placebo, 12 patients receiving 0.5 mg/d of rasagiline, and 13 patients receiving 1.0 mg/d of rasagiline; and supine: 27 patients receiving placebo, 17 patients receiving 0.5 mg/d of rasagiline, and 10 patients receiving 1.0 mg/d of rasagiline). There were no significant group differences in the incidence of decreased blood pressure compared with baseline. There were no significant group differences in the incidence of observed changes in blood pressure from supine to standing or in reports of symptomatic orthostasis as an adverse event. There were no significant group differences in laboratory values or ECG results during treatment. Home blood pressure monitoring before and after the main meal of the day (4809 observations at baseline, 4645 observations at week 3, and 4069 observations at week 26) showed no significant group differences. During treatment, dermatologic examinations revealed 3 patients with melanomas (1 pa-

tient receiving 0.5 mg/d rasagiline and 2 patients receiving 1.0 mg/d rasagiline). In addition, 1 patient was identified as having a melanoma before initiating study medication.

COMMENT

Rasagiline treatment was well tolerated and was associated with several therapeutic benefits in PD patients with motor fluctuations, despite optimized levodopa, including decreased off time on home diaries completed by patients and improvement in clinical global impression performed by blinded examiners. Neurological function improved during off times (ADL scores based on patient reports) and during on times (overall motor, postural instability and gait, rigidity, bradykinesia, and tremor scores based on patient reports and direct examination). These benefits were measurable at the first efficacy assessment 6 weeks after treatment was initiated and were sustained throughout the treatment period. Benefits tended to be greater in patients treated with 1.0 mg/d of rasagiline compared with 0.5 mg/d of rasagiline, but differences between the 2 rasagiline dosages were not significant for most end points. These results demonstrate a benefit of adding rasagiline to the regimens of patients who were already optimally treated with levodopa, dopamine agonists, amantadine, anticholinergics, and entacapone before enrolling in the study.

The lack of benefit demonstrated by the PDQUALIF scale does not override the benefits seen using patient-derived and examination-based end points. Although the PDQUALIF scale strives to assess the effects of PD on the patient's quality of life from the patient's point of view, it is not clear from existing research that this scale or any other existing quality-of-life scale has adequate psychometric properties to be considered a prerequisite for meaningful benefits.¹⁹ To date, most phase 3 studies in PD have used data from patient diaries or neurological examinations as their primary end points.

Observed decreases in daily off time were associated with nearly equal increases in on time. Patients treated with 0.5 mg/d of rasagiline experienced this benefit without extra time spent with troublesome dyskinesias. In patients treated with 1.0 mg/d of rasagiline, the increase in on time was greater and most of the increase was without troublesome dyskinesias, but 32% of the increase in-

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cluded troublesome dyskinesias. The UPDRS rating of dyskinesias also suggested that patients treated with 1.0 mg/d rasagiline experienced more dyskinesias than those treated with 0.5 mg/d rasagiline, but both groups re-

ported increased dyskinesias as adverse events in 18% of patients compared with 10% of the placebo group. Together with hints of a dose response favoring the higher dosage of rasagiline, these results suggest that the higher

dosage of rasagiline used in this study may have benefits that are partially offset by increased dyskinesias. In clinical practice, some of the dyskinesias might have been avoided by adjusting levodopa and other antiparkinsonian medications, but such changes were prohibited in the research setting because they might have confounded interpretation of rasagiline effects. Despite these restrictions, dyskinesias did not lead to early terminations. Other adverse effects, including gastrointestinal effects, may also be dose related. Psychiatric adverse effects that occur with dopaminergic therapies, such as hallucinations, somnolence, and confusion,²³⁻²⁶ were not increased by rasagiline.

The incidence of melanomas appears to be increased in PD patients based on epidemiological studies.^{16,17} On noting a few melanomas during the rasagiline development program,¹² routine dermatological examinations were incorporated into the study activities to improve surveillance. This may have resulted in an apparent increase in melanoma incidence because of improved ascertainment compared with other studies. Although the melanomas detected after starting the study drug occurred in patients receiving rasagiline, this is not particularly revealing because only one third were receiving placebo. Furthermore, the fact that 1 patient had a melanoma detected before starting the study drug supports the interpretation that these results were affected by increased surveillance of a disorder common to this patient group rather than being related to rasagiline exposure.

Other adjunctive, antiparkinsonian medications have been studied in similar trials, providing comparable results. Changes in on and off time as measured by patient diaries have been a standard measure of drug efficacy in these patients.²⁷ The catechol-*O*-methyl-transferase inhibitor entacapone, for example, improved on time by approximately 1 hour in PD patients with motor fluctuations when taken with each dose of levodopa.²³ Dopamine agonists, including pergolide mesylate,²⁴ pramipexole,²⁵ and ropinirole hydrochloride,²⁶ have added 1 to 2 hours of on time, although adverse effects have been more limiting than with rasagiline. Common adverse effects with these agents include gastrointestinal intolerance, hallucinations, edema, somnolence, and orthostatic hypotension, often resulting in discontinuation of the drug. The MAO inhibitor selegiline hydrochloride has not been carefully studied with respect to on-off fluctuations in PD.

Given the improvements in PD signs and symptoms during rasagiline monotherapy in patients with early PD^{11,12} and during adjunctive therapy in patients with motor fluctuations, rasagiline appears to be a promising new treatment for PD. The simplicity of administration (once-daily dosing with no titration required) and excellent tolerability of rasagiline are additional advantages. In addition to these short-term effects, rasagiline appears to have more long-lasting benefits, suggesting that it may modify the course of PD progression. Preclinical studies^{28,29} have shown that MAO-B inhibitors can protect neurons from oxidative stress, apoptosis, and other forms of injury in multiple experimental models. Furthermore, in a blinded study of 404 patients with early PD, those who

were randomized to rasagiline treatment for 12 months had better UPDRS scores than patients who were randomized to delay rasagiline treatment for the first 6 months.¹² Both groups were examined while taking the same dosage of rasagiline, so they should have been receiving the same symptomatic benefits; the sustained difference observed may be related to protective effects associated with long-term use. Further studies are warranted to explore this possibility.

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REFERENCES

- Ahlskog JE. Medical treatment of later-stage motor problems of Parkinson's disease. *Mayo Clin Proc.* 1999;74:1239-1254.
- Albin RL, Frey KA. Initial agonist treatment of Parkinson disease: a critique. *Neurology.* 2003;60:390-394.
- Lees AJ, Shaw KM, Kohout LJ, et al. Deprenyl in Parkinson's disease. *Lancet.* 1977;2:791-795.
- Schachter M, Marsden CD, Parkes JD, Jenner P, Testa B. Deprenyl in the management of response fluctuations in patients with Parkinson's disease on levodopa. *J Neurol Neurosurg Psychiatry.* 1980;43:1016-1021.
- Heinonen EH, Rinne UK, Tuominen J. Selegiline in the treatment of daily fluctuations in disability of parkinsonian patients with long-term levodopa treatment. *Acta Neurol Scand Suppl.* 1989;126:113-118.
- Golbe LI, Lieberman AN, Muentner MD, et al. Deprenyl in the treatment of symptom fluctuation in advanced Parkinson's disease. *Clin Neuropharmacol.* 1988; 11:45-55.
- Ulm G, Fornadi F. R(-)-deprenyl in the treatment of end-of-dose akinesia. *J Neural Transm Suppl.* 1987;25:163-172.
- Yahr MD, Elizan TS, Moros D. Selegiline in the treatment of Parkinson's disease: long term experience. *Acta Neurol Scand Suppl.* 1989;126:157-161.
- Hubble JP, Koller WC, Waters C. Effect of selegiline dosing on motor fluctuations in Parkinson's disease. *Clin Neuropharmacol.* 1993;16:83-87.
- Sterling J, Veinberg A, Lerner D, et al. (R)(+)-N-propargyl-1-aminoinadan (rasagiline) and derivatives: highly selective and potent inhibitors of monoamine oxidase B. *J Neural Transm Suppl.* 1998;52:301-305.
- Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol.* 2002;59:1937-1943.
- Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol.* 2004;61:561-566.
- Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;17:427-442.
- Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of subjects for the clinician. *J Psychiatr Res.* 1975; 12:189-198.
- Beck AT. *Beck Depression Inventory.* San Antonio, Tex: Psychological Corp; 1987.
- Moller H, Mellemkjaer L, McLaughlin JK, Olsen JH. Occurrence of different cancers in patients with Parkinson's disease. *BMJ.* 1995;310:1500-1501.
- Vanacore N, Spila-Alegiani S, Raschetti R, Mecco G. Mortality cancer risk in parkinsonian patients: a population-based study. *Neurology.* 1999;52:395-398.
- Fahn S, Elton RL; Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CO, Calne DB, Goldstein M, eds. *Recent Development in Parkinson's Disease.* Vol 2. Florham Park, NJ: Macmillan Health Care Information; 1987:153-164.
- Welsh M, McDermott MP, Holloway RG, et al; Parkinson Study Group. Development and testing of the Parkinson's disease quality of life scale. *Mov Disord.* 2003;18:637-645.
- Schwab RS, England AC Jr. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML, eds. *Third Symposium on Parkinson's Disease, Held at the Royal College of Surgeons of Edinburgh on 20, 21 and 22 May 1968.* Edinburgh, Scotland: E & S Livingstone; 1969:152-157.
- Hochberg Y. A sharper Bonferroni procedure for multiple significance testing. *Biometrika.* 1988;75:800-802.
- Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika.* 1976;63:655-660.
- Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. *Ann Neurol.* 1997;42:747-755.
- Olanow CW, Fahn S, Muentner M, et al. A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. *Mov Disord.* 1994;9:40-47.
- Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology.* 1997;49:162-168.
- Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. *Neurology.* 1998;51:1057-1062.
- Korczyn AD, Nussbaum M. Emerging therapies in the pharmacological treatment of Parkinson's disease. *Drugs.* 2002;62:775-786.
- Goetz ME, Breithaupt W, Sautter J, et al. Chronic TVP-1012 (rasagiline) dose-activity response of monoamine oxidases A and B in the brain of the common marmoset. *J Neural Transm Suppl.* 1998;52:271-278.
- Finberg JP, Takeshima T, Johnston JM, Commissiong JW. Increased survival of dopaminergic neurons by rasagiline, a monoamine oxidase B inhibitor. *Neuroreport.* 1998;9:703-707.